Comparative Effectiveness and Safety of Four Second line Pharmacological Strategies in Type 2 Diabetes (CER-4-T2D) Study: Programming Protocol

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Note

For a list of the main design and analytical revisions to the original CER-4-T2D study proposal, please see paragraph 12, page 17.

Date: 12/27/2021

1. **OBJECTIVE**: To design an observational analysis to emulate a target trial (i.e., a hypothetical pragmatic trial that would have answered the causal question of interest) comparing the effectiveness and safety of sodium-glucose cotransporter-2 inhibitors (SGLT2i), glucagon-like peptide 1 receptor agonists (GLP-1RA), dipeptidyl peptidase-4 inhibitors (DPP-4i), and sulfonylureas (SU), at the class and individual agent level, in head-to-head comparisons in patients with type 2 diabetes (T2D) and low or moderate cardiovascular risk.

Table 1.1 Specification and emulation of a target trial of second-line antidiabetic agents using real-world data from the US and the UK

Component	Target trial	Emulated trial using real-world data - CER-4-T2D Study -
Aim	To compare the effectiveness and safety of SGLT2i, GLP-1 RA, DPP-4i and SU at the class and individual agent level, in head-to-head comparisons	Same
Eligibility	Adults with continuous enrollment in database, who are at least 18 years old with a diagnosis of T2D at low or moderate risk of cardiovascular disease, who use metformin and have no history of type 1 diabetes, secondary or gestational diabetes, end-stage renal disease, pancreatitis, cirrhosis, MEN-2, organ transplant or insulin use.	Same, except criteria are assessed within one year on or before cohort entry (see Section "3. STUDY COHORT")
Treatment strategies	1. initiate SGLT2i 2. initiate GLP-1 RA 3. initiate DPP-4i 4. initiate SU	Same (see section "4. EXPOSURE")
Treatment assignment	Patients are randomly assigned to any of the 4 treatment strategies	Patients are assigned to treatment based on prescriptions filled (or issued by general practitioners). Randomization is emulated through adjustment for an

		extensive list of baseline covariates and statistical adjustment using propensity scores.
Follow-up	Follow-up starts at treatment assignment and ends at diagnosis of safety/effectiveness outcome, death, or loss to follow-up.	Follow-up starts at the date of initiation of treatment and ends at diagnosis of safety/effectiveness outcome, death, end of continuous health plan enrollment/end of registration with general practitioner, discontinuation of index exposure, addition/switch to other anti-diabetic medications, or end of study period (administrative end of follow-up), occurrence of bariatric surgery, whichever occurs first (see section "7. STUDY FOLLOW-UP AND CENSORING REASONS").
Outcome	List of efficacy and safety outcomes	List of effectiveness and safety outcomes (see section "5. OUTCOMES")
Causal contrast	Intention-to-treat effect, i.e., effect of being assigned to treatment with SGLT2i vs. GLP-1 RA vs DPP4i vs SU at baseline, regardless of whether individuals received treatment assigned after baseline.	On-treatment exposure definition in primary analyses to limit exposure misclassification during follow-up which is common in real-world evidence studies (see section "8. STATISTICAL ANALYSIS")
Statistical analysis	Intention-to-treat analysis, i.e., comparison of risk of efficacy/safety outcomes under each treatment strategy under the assumption that loss to follow-up did not introduce bias	On-treatment exposure definition with adjustment for baseline characteristics (see sections "6. COVARIATES" and "8. STATISTICAL ANALYSIS").

2. DATA SOURCES:

To emulate the specified target trial, we will use the following databases:

2.1. Optum Clinformatics – April 1, 2012 to latest available data

See description in paragraph 2.2.

2.2. IBM MarketScan – April 1, 2012 to latest available data

Optum and MarketScan databases are two U.S. research claims databases that primarily include adults with employer-based health plans, with nationwide coverage for over 60 million Americans, and meaningful numbers of patients ≥65 years from Medicare Advantage plans, employer-sponsored plans covering seniors, and Medicare supplemental insurance plans. Information is available on demographics, health plan enrollment status, inpatient and outpatient diagnoses and procedures, and pharmacy dispensing records, including medication start and refill, strength, quantity, and days' supply. Laboratory test results (e.g., A1C) are available for 40-45% of patients in Optum and 5-10% in MarketScan. Mortality data are available in Optum from CMS, Social Security Administration Master Death Files, in-hospital deaths, and death as a reason for insurance discontinuation, and in MarketScan from in-hospital deaths. Both have been extensively used in pharmacoepidemiologic research.

2.3. Medicare fee-for-service (FSS) – April 1, 2012 to latest available data

A U.S. federal health insurance program providing medical and prescription drug coverage to individuals aged 65 years and older and to younger individuals with disabilities. The Medicare program currently covers approximately 50 million Americans. The Medicare FFS claims database includes longitudinal, individual-level data on healthcare utilization, inpatient and outpatient diagnoses, diagnostic tests and procedures, and pharmacy filled prescriptions. Information on the date and cause of death is available through linkage with the Vital Status and the National Death Index (NDI) files. These data are widely used to study real-world drug effectiveness and safety.

2.4. Medicare FFS-RPDR – April 1, 2012 to latest available data

The Partners Research Patient Data Repository (RPDR) captures longitudinal EHR data for all patients that receive care at 2 large health care provider networks in the Boston metropolitan area. It contains information on BMI, blood pressure, smoking status, laboratory, and radiology test results. Members of our research team have deterministically linked about 550,000 patients by beneficiary numbers, date of birth, and sex with Medicare claims (success rate, 99.2%), and have used this infrastructure for epidemiologic research.

2.5. UK Clinical Practice Research Datalink (CPRD) – Jan 1, 2013 to latest available data

The CPRD is comprised of two large, computerized databases of longitudinal primary care records, GOLD and Aurum, for >50 million patients, shown to be representative of the general U.K. population. The CPRD includes data on diagnoses, procedures, prescription drugs, laboratory values, clinical measurements, e.g., blood pressure and BMI, and lifestyle characteristics, e.g., smoking status and alcohol use. These variables have been validated and data and practices are audited regularly to ensure high data quality. Information on hospital admissions, including diagnoses and procedures, is available through linkage with the U.K. Hospital Episode Statistics database. Information on mortality, including causes of death, is available through linkage with the Office for National Statistics.

2.6. U.S. National Veterans Health Administration (VHA) – April 1, 2012 to latest available data

The VHA is the largest integrated national health system, serving over 12 million U.S. Veterans. The VHA database includes demographic, diagnostic and procedure information from inpatient and outpatient encounters. Pharmacy data include medication name, date filled, days supplied, and number of pills dispensed. Laboratory results and vital signs data (e.g., outpatient measurements of height, weight, and blood pressure) are available from VHA clinical sources. Information on dates and cause of death are available through linkage with the vital status and the NDI files. The VHA database has provided data for several high-impact studies on diabetes treatment.

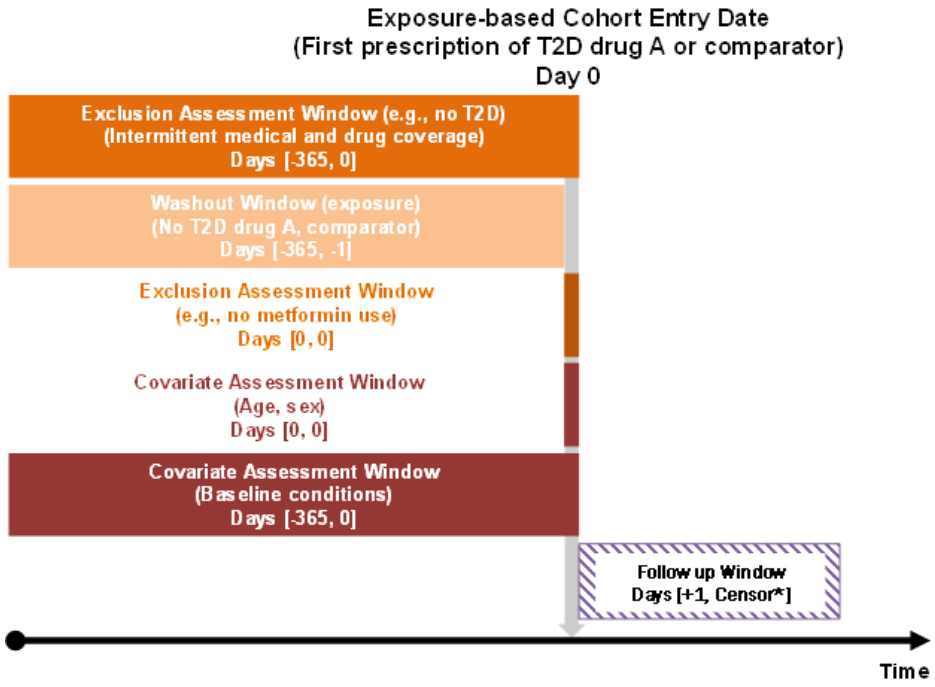
Note

We will conduct sequential analyses in year 1, 2 and 3 of the research project where we will update the data to maximize the sample size by the end of the funding period.

3. STUDY COHORT:

3.1. Design diagram

Figure 1. General study design of the CER-4-T2D study.



Note

Covariate assessment window for CRPD data is defined using all available lookback from on or before cohort entry.

3.2. Cohort entry (Day 0) is the day of the first fill or prescription with a second-line T2D medication. Follow-up for study outcomes will begin on the day after cohort entry (**Figure 1**).

3.3. Inclusion criteria (detailed definitions are reported in the **Table a1** of the **Appendix**):

1) Age ≥ 18 years for Optum Cliniformatics, IBM Marketscan, CPRD, and VHA, and ≥ 65 years for Medicare FFS at cohort entry
2) At least 12 months of continuous health plan enrollment (only claims) or registration with a general practitioner (CPRD) before and including cohort entry
3) Diagnosis of T2D within 12 months before (or ever before in CPRD) and including cohort entry
4) Low or moderate cardiovascular (CV) risk at cohort entry *****
5) Metformin maintenance therapy, defined as 2 fills (or prescriptions in CPRD) of metformin recorded within 6 months before and including cohort entry

Note

***** In an initial stage, we will restrict to patients at low/moderate CV risk (relatively to a population with T2D) by removing patients with a diagnosis code of established CV diseases recorded within 12 months prior to (or ever before in CPRD) and including cohort entry (see Table a1 in the Appendix for definitions of CV diseases). In parallel, we will build a prediction model to capture the granularity of CV risk. In a second stage, after completion and validation of the prediction model, we will use the predicted risks to identify and include patients at low/moderate CV risk. See paragraph 11, page 17, for further details on the prediction model.

3.4. Exclusion criteria (detailed definitions are reported in **Appendix Table a1**):

1) Missing age or gender information
2) Nursing care admission within 12 months before and including cohort entry (criteria ignored in CPRD)
3) Diagnosis of type 1 diabetes within 12 months before and including cohort entry
4) Diagnosis of secondary or gestational diabetes within 12 months before and including cohort entry
5) Any insulin fill or prescription within 12 months before and including cohort entry
6) Diagnosis of end stage renal disease (stage ≥ 5) within 12 months before and including cohort entry
7) Diagnosis of acute or chronic pancreatitis within 12 months before and including cohort entry
8) Diagnosis of cirrhosis or acute hepatitis within 12 months before and including cohort entry
9) Diagnosis of MEN-2 within 12 months before and including cohort entry
10) Recorded solid organ transplant code within 12 months before and including cohort entry
11) Patients with recorded initiation of more than one agent within a comparator class at cohort entry

Note

For CPRD data, the assessment window for exclusion criteria 3) to 10) is defined using all available lookback from on cohort entry.

4. EXPOSURE:

Definitions of new initiation and washout period described in the comparison **#4.1** will apply to all the comparisons listed in the "EXPOSURE" section. The final definitions for each drug class might change based on feasibility findings on the frequency of use of individual agents.

ONE-TO-ONE COMPARISONS AMONG SLGT-2 INHIBITORS (SGLT-2i), DPP-4 INHIBITORS (DPP4i) AND GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS (GLP-1 RA) [#4.1, #4.2, #4.3]

4.1. SGLT-2i vs DPP4i

4.1.1. Exposure:

New initiation of SGLT-2i listed in **Table 1**. New initiation is defined as no fill or prescription for any SLGT-2i within 12 months prior to cohort entry (washout period). New SGLT-2i users are not allowed to receive any DPP4i fill or prescription within 12 months before the new SGLT-2i initiation.

Table 1. List of SGLT-2 inhibitors

CANAGLIFLOZIN
CANAGLIFLOZIN/METFORMIN HCL
DAPAGLIFLOZIN PROPANEDIOL/METFORMIN HCL
DAPAGLIFLOZIN PROPANEDIOL
EMPAGLIFLOZIN
EMPAGLIFLOZIN/METFORMIN HCL

ERTUGLIFLOZIN PIDOLATE/METFORMIN HCL
ERTUGLIFLOZIN PIDOLATE
EMPAGLIFLOZIN/LINAGLIPTIN
EMPAGLIFLOZIN/LINAGLIPTIN/METFORMIN HCL
DAPAGLIFLOZIN PROPANEDIOL/SAXAGLIPTIN HCL
ERTUGLIFLOZIN PIDOLATE/SITAGLIPTIN PHOSPHATE

4.1.2.Referent:

New initiation of DPP4i listed in **Table 2**. New initiation is defined as no prescription fill for any DPP4i within 12 months prior to cohort entry (washout period). New DPP4i users are not allowed to receive any SGLT-2i fill or prescription within 12 months before the new DPP4i initiation.

Table 2. List of DPP4 inhibitors

ALOGLIPTIN BENZOATE/METFORMIN HCL
ALOGLIPTIN BENZOATE
ALOGLIPTIN BENZOATE/PIOGLITAZONE HCL
SAXAGLIPTIN HCL
SAXAGLIPTIN HCL/METFORMIN HCL
LINAGLIPTIN
LINAGLIPTIN/METFORMIN HCL
SITAGLIPTIN PHOSPHATE/METFORMIN HCL
SITAGLIPTIN PHOSPHATE
SITAGLIPTIN PHOSPHATE/SIMVASTATIN
DAPAGLIFLOZIN PROPANEDIOL/SAXAGLIPTIN HCL
EMPAGLIFLOZIN/LINAGLIPTIN
EMPAGLIFLOZIN/LINAGLIPTIN/METFORMIN HCL
ERTUGLIFLOZIN PIDOLATE/SITAGLIPTIN PHOSPHATE

4.2. SGLT-2i vs GLP-1 RA

Please replace the referent group with initiators of GLP-1 RA listed in **Table 3**.

Table 3. List of GLP-1 RA

INSULIN DEGLUDEC/LIRAGLUTIDE*
INSULIN GLARGINE, HUMAN RECOMBINANT ANALOG/LIXISENATIDE*
LIXISENATIDE
LIRAGLUTIDE
DULAGLUTIDE
SEMAGLUTIDE
ALBIGLUTIDE
EXENATIDE MICROSPHERES
EXENATIDE

* Combinations with insulin might be added to the definition of GLP-1ra for the sensitivity analyses of comparative safety evaluations.

4.3. GLP-1RA vs. DPP-4i

Please replace the exposure group with initiators of GLP-1 RA listed in **Table 3** and the referent group with initiators of DPP4i listed in **Table 2**.

ONE-TO-ONE COMPARISONS WITH SULFONYLUREA (SU) [#4.4, #4.5, #4.6]

4.4. SGLT-2i vs SU

Please replace the referent group with initiators of 2nd generation SU listed in **Table 4**.

Table 4. List of 2nd generation SU

PIOGLITAZONE HCL/GLIMEPIRIDE
ROSIGLITAZONE MALEATE/GLIMEPIRIDE
GLIPIZIDE/METFORMIN HCL
GLYBURIDE,MICRONIZED
GLYBURIDE/METFORMIN HCL
GLIMEPIRIDE
GLYBURIDE
GLIPIZIDE

4.5. GLP1RA vs. SU

Please replace the exposure group with initiators of GLP-1 RA listed in **Table 3** and the referent group with initiators of SU listed in **Table 4**.

4.6. DPP41 vs. SU

Please replace exposure group with initiators of DPP4i listed in **Table 2** and referent group with initiators of SU listed in **Table 4**.

N-WAY COMPARISONS [#4.7, #4.8, #4.9, #4.10]

4.7. SGLT2i vs. GLP-1RA vs. DPP-4i vs. SU (4-way comparison)

Initiators of DPP4i, listed in **Table 2**, are considered the referent group for the 4-way comparison. Further details are reported in the statistical analysis (section b of the paragraph 8.1.2)

4.8. SGLT2i vs. GLP-1RA vs. DPP-4i (3-way comparison)

Initiators of DPP4i, listed in **Table 2**, are considered the referent group for the 3-way comparison. Further details are reported in the statistical analysis (section b of the paragraph 8.1.2)

4.9. Canagliflozin vs. Dapagliflozin vs. Empagliflozin (within-SGLT2i class n-way comparison)

The referent and exposure groups will be selected through a feasibility analysis on the frequencies of index drugs and outcome events. Further details are reported in the statistical analysis (section b of the paragraph 8.1.2)

4.10. Dulaglutide vs. Exenatide vs. Liraglutide vs. Semaglutide (within-GLP-1RA class n-way comparison)

The referent and exposure groups will be selected through a feasibility analysis on the frequencies of index drugs and outcome events. Further details are reported in the statistical analysis (section b of the paragraph 8.1.2)

Note

Inter-class comparisons of individual agents will be informed by findings from both 1:1 pairwise comparisons between classes and within-class comparisons of individual agents. Pre-specified contrasts of interest include comparison between the individual agents belonging to SGLT2i and GLP-1RA (e.g., empagliflozin vs. liraglutide). Further comparisons between individual agents, that are not currently listed in the protocol, might be investigated whether it is needed.

5. OUTCOMES

5.1. Effectiveness outcomes

Primary effectiveness outcomes are MACE, modified MACE, and hospitalization for heart failure (see **Table a2** in the **Appendix** for detailed definitions). Secondary effectiveness outcomes are myocardial infarction, stroke, CV mortality, all-cause mortality, coronary revascularization, chronic kidney disease (CKD) progression, kidney replacement therapy, kidney death, kidney failure, early kidney disease, glycemic control, weight loss or gain (see **Table a3** of the **Appendix** for detailed definitions).

Outcome	Databases				
	Optum	MarketScan	Medicare FFS	CPRD	VHA
MACE Myocardial Infarction, Stroke, CV mortality			Yes	Yes	Yes
Modified MACE Myocardial Infarction, Stroke, All-Cause mortality	Yes	Yes	Yes	Yes	Yes
Hospitalization for heart failure	Yes	Yes	Yes	Yes	Yes
Myocardial Infarction	Yes	Yes	Yes	Yes	Yes
Stroke	Yes	Yes	Yes	Yes	Yes
CV mortality			Yes	Yes	Yes
All-cause mortality	Yes	Yes	Yes	Yes	Yes
Coronary revascularization	Yes	Yes	Yes	Yes	Yes
CKD progression * Sustained decrease in eGFR, KRT (maintenance dialysis and kidney transplantation), kidney death				Tentative	Yes
Sustained decrease in eGFR *	Tentative			Tentative	Yes
KRT *	Yes	Yes	Yes	Yes	Yes
Kidney death *			Yes	Yes	Yes
Kidney failure * (sustained eGFR <15 ml/min/1.73m2, maintenance dialysis and kidney transplant)	Tentative			Tentative	Yes
Early kidney disease * Defined by change in eGFR in patients with baseline eGFR > 60	Tentative			Tentative	Yes
Glycemic control Defined by HbA1c change in patients with available baseline HbA1c	Tentative			Yes	Yes

Insulin initiation	Yes		Yes	Yes	Yes
Weight loss or gain * Defined by weight change in patients with available baseline weight				Yes	Yes

Outcome analyses noted as "tentative" will require ad hoc investigation in corresponding databases to determine the likelihood of validity and thus the capacity of these databases to contribute to overall pooled estimates.
* exploratory outcome since no validated claim-based outcome definition is currently available. We will consider additional components/measures whether necessary.
Abbreviations: CKD, chronic kidney disease; KRT, kidney replacement therapy

5.2. Safety outcomes

Detailed definitions are reported in the **Table a4** of the **Appendix**.

Outcome	**Exposure of interest**	**Databases**				
		Optum	**MarketScan**	**Medicare FFS**	**CPRD**	**VHA**
Diabetic ketoacidosis	SGLT-2i	Yes	Yes	Yes	Yes	Yes
Bone fractures	SGLT-2i	Yes	Yes	Yes	Yes	Yes
Lower-limb amputations	SGLT-2i	Yes	Yes	Yes	Yes	Yes
Acute kidney injury	All drug classes	Yes	Yes	Yes	Yes	Yes
Urinary infections	SGLT-2i	Yes	Yes	Yes	Yes	Yes
Genital infections	SGLT-2i	Yes	Yes	Yes	Yes	Yes
Acute pancreatitis	GLP1 RA, DPP4i	Yes	Yes	Yes	Yes	Yes
Biliary events	GLP1 RA, DPP4i	Yes	Yes	Yes	Yes	Yes
Severe hypoglycemia	SU	Yes	Yes	Yes	Yes	Yes
Short-term retinopathy progression *	GLP1 RA	Yes	Yes	Yes	Yes	Yes
Safety signals identified via TreeScan ^						

* exploratory outcomes since no validated claim-based outcome definition is currently available.
^ see section 9 of the protocol.

5.3. Other outcomes

Outcome	**Databases**				
	Optum	**MarketScan**	**Medicare FFS**	**CPRD**	**VHA**
Home time Time spent out of hospital and skilled nursing facility ^ Time to Nursing Home Placement ^^			Yes		
Medication persistence Time to discontinuation	Yes	Yes	Yes	Yes	Yes
Switching patterns Treatment trajectories: patterns of use following initiation of treatment under study. To be illustrated using concentric circle diagrams or Sankey diagrams as appropriate.	Yes	Yes	Yes	Yes	Yes

^ Lee H, Shi SM, Kim DH. Home Time as a Patient-Centered Outcome in Administrative Claims Data. J Am Geriatr Soc. 2019 Feb;67(2):347-351

^^ Kim DH, Li X, Bian S, Wei LJ, Sun R. Utility of Restricted Mean Survival Time for Analyzing Time to Nursing Home Placement Among Patients with Dementia. JAMA Netw Open. 2021 Jan 4;4(1):e2034745.

6. COVARIATES

The overall list of covariates is reported in **Table a5** of the Appendix. Specific set of covariates will be selected from the overall list based on the outcome investigated. Covariates will be assessed at baseline (i.e., within 12 months prior to and including cohort entry date) for all databases, except for CPRD, which will consider all available lookback available within the database. Definitions are available upon request.

7. STUDY FOLLOW-UP AND CENSORING REASONS

Using an "on-treatment approach" as main analysis of the comparisons listed in paragraph **4**, please follow eligible individuals from the day after cohort entry until the first occurrence of:

1) Effectiveness/safety study outcome,
2) End of the study period (administrative end of follow-up),
3) End of continuous health plan enrollment (only claims) or end of registration with general PR actioners (CRPD),
4) Index exposure/referent discontinuation (grace period of 60 days, unless otherwise noted),
5) Addition/switching to the other treatment group,
6) Switching to anti-diabetic medications other than the study drugs,
7) Bariatric surgery,
8) Death.

8. STATISTICAL ANALYSIS

8.1. Primary analyses

All the steps listed in this paragraph will be followed for each of the study cohort created based on eligible criteria and comparison of interest (See sections "**3. STUDY COHORT"** and "**4. EXPOSURE"**).

8.1.1. Descriptive analysis (before adjustment)

- Please create the study cohort following inclusion and exclusion criteria stated above (See paragraph "3. STUDY COHORT") and selecting the appropriate comparison of interest (See paragraph "4. EXPOSURE").
- Please summarize the baseline patient characteristics (See paragraph 6) by index drug using descriptive statistics (frequencies, means, medians) *before adjustment*. Please create separate summary tables for each data source.
- Please calculate and report numbers of events, person-years, incidence rates with 95% confidence intervals (CI) and rate differences with 95% CI of the outcome of interest.

8.1.2. Achieving balance in patient covariates (adjustment)

Please use propensity score (PS) methodology to address confounding by indication.

a. *Pairwise comparisons of T2D drug classes*:

- Please calculate PS for each pairwise comparison as the predicted probability of receiving one class vs. another, conditional upon a set of potential confounders (See Table a5 in the Appendix) using a multivariable logistic regression model.
- Please use the resulting PS to match patients in a 1:1 ratio using a nearest-neighbor algorithm with a maximum caliper of 0.01 of the PS (restricting analyses to those patients who share common distribution with respect to potential indications and contraindications).
- When exposure prevalence is low and outcomes are rare, we will consider using PS-based fine stratification creating unequally sized propensity-score strata, after ranking only the exposed patients based on the PS and assigning unexposed patients to these strata based on their PS (*propensity score strata exposed approach*). SAS macros for propensity score stratification are available at: http://www.drugepi.org/dope-downloads/.

b. *N-way comparisons of T2D drug classes or agents*:

- We will consider using weighting methods to reweight both exposed and unexposed groups to balance patient characteristics. Weighting methods can naturally generalize to a non-dichotomous treatment variable, including three or more treatment groups.[1,2] Please use the example code available on https://github.com/kaz-yos/mw

8.1.3.Diagnostics of achieved balance (after adjustment)

- Please create a summary table stratified by index drug of the baseline patient characteristics listed in "6. COVARIATES", using descriptive statistics (frequencies, means, medians) *after adjustment*. Please create separate summary tables for each data source.
- Please inspect covariate balance before and after PS-adjustment by calculating standardized differences for each covariate (including characteristics only measured in a subset of the claims-only populations and thus not included in main PS model, see Table a5 in the Appendix).
- Please inspect overlap in PS distributions before and after adjustment (plots) and assess the post-matching c-statistic from the PS model refit in the matched sample, which is expected to be closer to 0.5 if balance has been achieved.[3]

8.1.4.Statistical analysis in the balanced study cohort

- Please calculate PS-matched numbers of events, person-years, incidence rates, hazard ratios (HRs), and rate differences (RDs), each with 95% CIs for the outcome of interest.
- Please use Cox proportional hazards models to estimate hazard ratios and 95% CI

- Please plot Kaplan-Meier curves of cumulative incidence and compare rates between treatment groups with log-rank tests
- For recurrent events of selected CV outcomes (e.g., HHF), we will consider using semiparametric proportional rates method of Lin and a joint gamma frailty model will be used to quantify the association between 2nd-line T2D agents and recurrent outcome events.

8.1.5. Pooling of database-specific estimates

- Please pool estimates from all databases using the DerSimonian and Laird random-effects model with inverse variance.[4] Please also pool estimate from all databases using a fixed-effects model as a sensitivity analysis.
- Please investigate between-dataset heterogeneity calculating the I^2 statistic and 95% CI.[5] Values above 50% will be considered evidence of substantial heterogeneity. If heterogeneity across datasets exceeds 50% as measured by I^2 statistic, we will investigate contribution to the overall heterogeneity of each database by removing one dataset in turn from the pooled analysis.

8.2. Sensitivity analyses

8.2.1. Assess and correct for residual confounding in main analyses

a. Assess balance and address potential imbalances

- *Search for balance*. Using available laboratory and EHR data in a subset of patients in the large claims databases (i.e., laboratory values in Optum and MarketScan; EHR data in Medicare FFS-RPDR), please evaluate the extent of imbalance after PS adjustment following the same methodology described in paragraph 8.1.3. If no imbalances remain, we will conclude that the main adjustment approach in claims data sufficiently addresses confounding.
- *In case of imbalance, search for differences in the results*. If imbalances remain, please repeat analyses within the subset with and without the additional laboratory information in the PS model. If inclusion of these variables in the model does not materially change the results, we will again conclude that the main adjustment approach sufficiently addresses confounding.
- *In case of differences in the results, consider applying **PS-calibration***. If inclusion of these variables changes the results, please use PS-calibration to address unmeasured confounding by calibrating the PS in the main study population based on a "gold-standard" PS built in the subset of the population that includes the unmeasured confounders. [6-8]

b. Negative and positive tracer outcomes

To increase confidence that the main analysis sufficiently addresses confounding and other biases, we will consider using:

i. ***Positive tracer outcomes***, for which we would expect a positive or negative association with the exposure,
ii. ***Negative tracer outcomes***, for which we would expect a null finding.

c. Quantitative bias analyses (i.e., defining the strength of a hypothetical unmeasured confounder which, if present, would explain the observed effect across a range of confounder prevalence measures in the treatment groups) to appraise the impact of any additional suspected source of unmeasured confounding.[9]

Note

If we cannot control for unmeasured confounding, we will disregard the database associated with higher likelihood for confounding.

8.2.2. High-dimensional PS

For databases that lack information for laboratory values (i.e., Optum and MarketScan) or EHR data (i.e., Medicare FFS-RPDR), we will consider using high dimensional PS approach to improve confounding adjustment by estimating the potential confounding for a large number (usually hundreds or thousands) of codes in the database. [10,11] This approach can adjust for variables that are proxies for confounders and that were not pre-specified risk factors for the outcomes of interest.

8.2.3. Testing robustness of on-treatment approach

To assess sensitivity of primary on-treatment estimated effects to potential informative censoring, we will conduct additional sensitivity analyses using:

i. ***Varying grace period after index exposure/referent discontinuation.*** We will consider applying shorter or longer grace periods (e.g., 30 or 90 days), after treatment discontinuation.
ii. ***Time-limited intention-to-treat (ITT) effect*** carrying forward the effect of the initiated T2D medication independently of discontinuation or switching. Please follow individuals from the day after cohort entry until the first occurrence of:
    1) Study outcome,
    2) End of the study period (or available data),
    3) End of continuous health plan enrollment,
    4) Death,
    5) 12 months after drug initiation.
iii. ***Inverse probability censoring weights (IPCW).*** To investigate the impact of informative censoring from drug switching/discontinuation, and to investigate death as a competing risk, we will use inverse probability of censoring weights to reweigh the cohorts. These weights will be calculated by subdividing the follow-up period into 30-day intervals and using logistic regression models to predict the probability of remaining uncensored in each interval, using time-varying variables measured in

the previous interval. Stabilized IPCWs will be combined with treatment weights generated in the primary analysis for a final weight to be used in the outcome model.

If sensitivity analyses **(i)** or **(ii)** indicate primary analyses are prone to informative censoring (e.g., 95% CI of primary estimates produced under the primary on-protocol scheme are non-overlapping with 95% CI of estimates produced under an ITT scheme or after the implementation of IPCW), then we will consider prioritization of results from ITT or IPCW analyses above primary on-treatment results to inform clinical decision making.

8.3. Secondary analyses

8.3.1. GRADE-like study population

To closely mimic the population included in the GRADE trial, please build a new cohort following inclusion and exclusion criteria listed in the paragraph "3. STUDY COHORT" except for inclusion criteria n. 4 and 5 which are replaced with:

a. Please ***modify criterion n. 4*** removing from the list of the CV codes in Table a1 of the Appendix: ACS unstable angina, stable angina, coronary atherosclerosis. This modification will be applied to the cohort definition until completion and validation od the CV prediction model (see paragraph 11)
b. Please ***modify criterion n. 5***, metformin maintenance therapy will be defined in the GRADE-like cohorts as 2 fills (or prescriptions in CPRD) of metformin **monotherapy** recorded within 6 months before and including cohort entry

8.3.2. Secondary analysis for safety outcomes

To test the informativeness of drug-related harms, please build a new cohort following inclusion and exclusion criteria listed in the paragraph "3. STUDY COHORT" except for:

a. Please **remove *inclusion criterion* n. 4)**, thus the cohort is not restricted to patients with low or moderate CV risk
b. Please **remove *inclusion criterion* n. 5)**, thus the cohort is not restricted to patients on baseline metformin
c. Please **remove *exclusion criterion* n. 5)** "Any insulin fill or prescription within 12 months before and including cohort entry", thus baseline use of insulin or other T2D medications is allowed as long as not art of the exposure definition.

8.4. Subgroup analyses

- Definition of potential effect modifiers. To assess potential effect modification, please conduct subgroup analyses for selected outcomes stratified by each subgroup of interest listed in **Table**

5. The variables defining the subgroups are measured at baseline (12 months prior to and including cohort entry date or, for CPRD data, any time before and including cohort entry date) or at cohort entry. Other subgroups might be considered based on further stakeholders' feedback.

- Achieving balance in patients' covariates and diagnostics of achieved balance. Within each category of the subgroup of interest (for example, within "male" and "female" categories of the subgroup "gender"), please re-estimate the PS for the exposure and referent drugs and re-perform the PS matching following all the steps reported in paragraphs 8.1.2 and 8.1.3.
- Statistical analysis in the balanced subgroup cohort. For each category of the subgroup of interest, please provide number of outcome events, person-years, incidence rates and final findings in both relative (i.e., hazard ratio, HR and 95% CI) and absolute scales (i.e., rate difference, RD and 95% CI) before and after adjustment following the steps described in paragraph 8.1.4.
- Testing treatment heterogeneity within subgroups. Finally, please estimate the presence of treatment heterogeneity across categories of the subgroup of interest by performing the Wald test for homogeneity on the relative and absolute scale.

Table 5. Proposed pre-specified patient subgroups of interest

Subgroup of interest	Categories	References
Age	65-74 years, 75+ years (Medicare) 18-64 years, 65+ years (Other databases)	--
Gender	Female, male	--
Race	White, black, others (Medicare and VA)	--
Baseline CV risk	In an initial stage, we will identify the presence of low/moderate vs. high CV risk in the study population and accordingly stratify the analysis, based on diagnosis codes of CV diseases measured at baseline. After completion and validation of a CV prediction model, we will use predicted risks to identify finer CV risk levels.	See paragraph 11 for further information on the development and validation of the CV prediction model
Chronic kidney disease (CKD)	We will stratify by CKD stages by using eGFR values or claims-based validated algorithms.	- Paik JM et al. Accuracy of identifying diagnosis of chronic kidney disease in administrative claims data. Manuscript accepted for publication in Pharmacoepidemiology and Drug Safety. Dec 12, 2021. In press. - Iwagami M et al. Validity of estimated prevalence of decreased kidney function and renal replacement therapy from primary care electronic health records compared with national survey and registry data in the United Kingdom. Nephrol Dial Transplant. 2017;32(suppl_2):ii142-ii150.
Frailty	We will stratify by frailty levels by using validated frailty index scores	- Kim DH et al. Measuring Frailty in Administrative Claims Data: Comparative Performance of Four Claims-Based Frailty Measures in the U.S. Medicare Data. J Gerontol A Biol Sci Med Sci. 2020;75(6):1120-1125.

		- Cheng D et al. Updating and Validating the Veterans Affairs Frailty Index: Transitioning from ICD-9 to ICD-10. J Gerontol A Biol Sci Med Sci. 2021;76(7):1318-1325. - Orkaby AR et al. The Burden of Frailty among US Veterans and its Association with Mortality, 2002-2012. J Gerontol A Biol Sci Med Sci. 2019;74(8):1257-1264. - Clegg A, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age Ageing. 2016;45(3):353-60.
Socioeconomical conditions	We will consider socioeconomical status categories available in Medicare and CPRD databases.	- Herrett E et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015;44(3):827-836. - Gopalakrishnan C et al. Evaluation of Socioeconomic Status Indicators for Confounding Adjustment in Observational Studies of Medication Use. CPT 2019; 105:1513-1521.

Abbreviations: CV, cardiovascular

8.5 Missing data

Missingness in EHR and laboratory data will be examined in terms of frequency and patterns of missingness and addressed via complete-case analysis strategy or missing indicator variable or multiple imputation methods, depending on the extent of missing information.[12,13] PS-calibration, as described above, will also be considered to assess the impact of missing data.[6-8]

9. TREES-BASED SCAN STATISTICS (TreeScan™)

In Medicare and one commercial database, we will consider identifying potential safety signals using tree-based scan statistics, a data mining approach implemented by the free TreeScan™ software (www.treescan.org). The wide range of health outcomes is arranged in a hierarchical tree constructed based on international classification of disease coding (ICD). The results will be adjusted for multiple testing.[14-18]

10. PREDICTION RULES

Guided by the results of the safety and Treescan analyses, we will estimate the individual patients' risk of selected drug-related harms associated with second-line T2D medications by developing and validating ***treatment-specific prediction rules*** following the steps below. Input from the Advisory Panel and the research team will be considered in prioritizing the prediction of specific harms over others.

1) Select potential predictors of drug-related adverse events based on previous literature, clinical experience, and expert opinion.
2) Build predictive models of drug-related adverse events considering several machine learning approaches, including least absolute shrinkage and selection operator (LASSO), and potential other approaches, e.g., gradient boosted model.
3) Train the models in bootstrap samples without replacement and test them in subjects not included in the bootstrap sample. [19]

4) Assess the performance of the machine learning modeling approaches using several metrics, such as Brier score, area under the receiver operating characteristic curve, and calibration plots.[20]
5) Build proportional hazards models including the outcome predictors identified by the most efficient machine learning modeling approach to produce coefficients that could be used to generate targeted scoring systems for assisting decision-making.
6) We will consider validating the prediction rules on a different database.

11. PREDICTION MODEL TO STRATIFY RISK OF CV DISEASE

In addition to using diagnosis codes of CV diseases measured at baseline, we plan to also stratify the study populations into levels of CV risk on the basis of their predicted risk of atherosclerotic CV disease and/or heart failure as estimated by prediction models. In order to do so, we plan to use the following approach:

1) Identify patients with type 2 diabetes mellitus patients, who have information from claims and electronic heath records (EHR) from the Medicare FFS-RPDR database. The cohort entry date will be any physician office or outpatient visit date.
2) Identify outcome of interest defined as atherosclerotic CV disease or hospitalization for heart failure (see definitions in Table a1 and a2 of the Appendix) during follow up (e.g., two years) starting from cohort entry.
3) Divide the study population into two subgroups: (i) one with baseline CV diseases (CVD) and (ii) one without baseline CVD, based on diagnosis codes listed in Table a1 of the Appendix.
4) Select potential predictors based on clinical knowledge using information from (i) claims + EHR data, and (ii) claims only.
5) Build predictive models using machine learning models, shown to work well in high-dimensional claims and in the presence of missing data: LASSO and gradient boosted model (XG-boost).
6) Train the models using 10-fold cross validation based on training and testing samples.[19]
7) Assess the performance of the machine learning models using Brier score, area under the receiver operating characteristic curve, and calibration plots.[20]
8) Compare the performance between approaches based on claims-only vs. claims + EHR variables, using precision-recall curves and decision curves to contrast the net benefit of the selected approaches, and reporting the observed probability of events by predicted risk deciles.[21,22]
9) Select the most influential predictors from these claims-based machine learning modelling approaches by relative influence measures or ranking the magnitude of coefficients and build proportional hazards models to produce coefficients that could be used to generate CV risk score.
10) Apply the risk prediction score on target databases to identify populations at different levels of CV risk.

12. CER-4-T2D revised analytical plan

We summarize below the main revisions to the original CER-4-T2D study proposal:

- To increase the representativeness of the study population included in the CER-4-T2D study, we plan not to exclude patients with a history of malignancies.

- To comply with the accelerated timeline of the CER-4-T2D study, we will prioritize the identification and inclusion in the analyses of patients at low/moderate CV risk on the basis of the absence of diagnosis codes indicative of established CV disease at baseline (i.e., pre-exposure). In a second stage, we will build a prediction model to capture the granularity of CV risk and will use the predicted risks to identify finer levels of CV risk.
- To account for the fact that individuals who undergo bariatric surgery during follow-up may no longer be eligible for type 2 diabetes (T2D) treatment, we plan to censor patients who undergo bariatric surgery during follow-up.
- To assess sensitivity of primary on-treatment estimated effects to potential informative censoring, we will consider varying the primary grace period.

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Appendix

*****Note******

- *The lowercase letter (**x**) acts as a general wildcard. It will replace a set of codes characterized by the same numbers or letters before or after the **x** (for example, 250.**x** includes all codes starting with 250.; 402.**x**1 includes 402.**0**1, 402.**1**11, 402.**9**1; etc.)*
- *Common abbreviations: MI, myocardial infarction; ACS, acute coronary syndrome; CV, cardiovascular;* MACE, *major adverse cardiovascular events; ICD, international classification of diseases.*

Table a1. Inclusion/exclusion criteria definitions

Inclusion criteria	Codes	Setting/Position
Type 2 diabetes mellitus	ICD 9 diagnosis: 250.00, 250.02, 250.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92 ICD 10 diagnosis: E11.x	Any setting, any position
Low or moderate CV risk **N.B.** **- TO DEFINE OUR PRIMARY COHORT PLEASE EXCLUDE PATIENTS WITH THE FOLLOWING CV CODES (see paragraph 3.3)** **- TO DEFINE GRADE-LIKE POPULATION PLEASE DO NOT INCLUDE IN THE LIST OF CV CODES: ACS UNSTABLE ANGINA, STABLE ANGINA, CORONARY ATHEROSCLEROSIS (see paragraph 8.3.1)**	**Acute MI** ICD-9 diagnosis: 410.x ICD-10 diagnosis: I21.x, I22.x **Old MI** ICD-9 diagnosis: 412 ICD-10 diagnosis: I25.2 **MI sequelae** ICD-9 diagnosis: 429.79 ICD-10 diagnosis: I23.x **ACS unstable angina** ICD-9 diagnosis: 411.1, 411.8x ICD-10 diagnosis: I20.0, I24.8, I24.9, I25.110, I25.7x0 **Stable angina** ICD-9 diagnosis: 413.xx ICD-10 diagnosis: I20.1, I20.8, I20.9, I25.11x, I25.7x1, I25.7x8, I25.7x9 **Coronary atherosclerosis** ICD-9 diagnosis: 414.xx, 429.2 ICD-10 diagnosis: I25.10, I25.3, I25.4x, I25.5, I25.6, I25.8x, I25.9 **Coronary procedure** ICD-9 PX: 00.66, 36.03, 36.06, 36.07, 36.09, 36.1x, 36.2x, 36.3x ICD-10 PX: 0210.xxx, 0211.xxx, 0212.xxx, 0213.xxx, 021K0Z5, 021K4Z5, 021L0Z5, 021L4Z5, 0270.xxx, 0271.xxx, 0272.xxx, 0273.xxx, 02C0.xxx, 02C1.xxx, 02C2.xxx, 02C3.xxx, 02QA.xxx, 02QB.xxx, 02QC.xxx CPT/HCPCS: 33140, 33141, 33510-33536, 33545, 33572, 92920, 92921, 92924, 92925, 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, 92944, 92973, 92980, 92980, 92981, 92984, 92995, 92996 **History of coronary procedure** ICD-9 diagnosis: V45.81, V45.82 ICD-10 diagnosis: Z95.1, Z95.5, Z98.61, I97.410, I97.411, I97.610, I97.611, I97.630, I97.631, I97.640, I97.641, T82.211x, T82.212x, T82.213x, T82.218x **Congestive heart failure** ICD-9 diagnosis: 428.xx, 398.91, 402.x1, 404.x1, 404.x3 ICD-10 diagnosis: I09.81, I11.0, I13.0, I13.2, I50.xxx, I97.13x	Any setting, any position

	Stroke ICD-9 diagnosis: 433.xx, 434.xx, 436 ICD-10 diagnosis: I63.xxx, I65.xx, I66.xx, G43.6x9, G46.3, G46.4 **Peripheral arterial disease** ICD-9 diagnosis: 440.2x, 440.3x, 440.4, 443.9 ICD-10 diagnosis: I70.x, I73.89, I73.9, T82.310x, T82.312x, T82.320x, T82.322x, T82.330x, T82.332x, T82.390x, T82.392x, T82.856x, Z98.62 ICD-9 procedure: 38.08, 38.18, 38.38, 38.48, 39.25, 39.29, 39.5x (excluding 39.53), 39.90, 39.91, 39.99 ICD-10 procedure: 0410096-99,0410496-99, 0470046, 0470056, 0470066, 0470076, 0470346, 0470356, 0470366, 0470376,0470446, 0470456, 0470466, 0470476, 04700E6, 04703E6, 04704E6,047E046, 047E056, 047E066, 047E076; 041009.x, 04100A.x, 04100J.x, 04100K.x, 04100Z.x, 041049.x, 04104A.x, 04104J.x, 04104K.x, 04104Z.x (where x=B,C,D,F,G,H,J,K,Q,R,6,7,8,9); 041C09.x, 041C0A.x,, 041C0J.x, 041C0K.x, 041C0Z.x, 041C49.x, 041C4A.x, 041C4J.x, 041C4K.x, 041C4Z.x, 041D09.x, 041D0A.x, 041D0J.x, 041D0K.x, 041D0Z.x, 041D49.x, 041D4A.x, 041D4J.x, 041D4K.x, 041D4Z.x, 041E09.x, 041E0A.x, 041E0J.x, 041E0K.x, 041E0Z.x, 041E49.x, 041E4A.x, 041E4J.x, 041E4K.x, 041E4Z.x, 041F09.x, 041F0A.x, 041F0J.x, 041F0K.x, 041F0Z.x, 041F49.x, 041F4A.x, 041F4J.x, 041F4K.x, 041F4Z.x, 041H09.x, 041H0A.x, 041H0J.x, 041H0K.x, 041H0Z.x, 041H49.x, 041H4A.x, 041H4J.x, 041H4K.x, 041H4Z.x, 041J09.x, 041J0A.x, 041J0J.x, 041J0K.x, 041J0Z.x, 041J49.x, 041J4A.x, 041J4J.x, 041J4K.x, 041J4Z.x (where x=J,K,H); 041K09.x, 041K0A.x, 041K0J.x, 041K0K.x, 041K0Z.x, 041K49.x, 041K4A.x, 041K4J.x, 041K4K.x, 041K4Z.x, 041L09.x, 041L0A.x, 041L0J.x, 041L0K.x, 041L0Z.x, 041L49.x, 041L4A.x, 041L4J.x, 041L4K.x, 041L4Z.x (where x=H,J,K,L,M,N,P,Q,S); 041M09.x, 041M0A.x, 041M0J.x, 041M0K.x, 041M0Z.x, 041M49.x, 041M4A.x, 041M4J.x, 041M4K.x, 041M4Z.x, 041N09.x, 041N0A.x, 041N0J.x, 041N0K.x, 041N0Z.x, 041N49.x, 041N4A.x, 041N4J.x, 041N4K.x, 041N4Z.x (where x=L,M,P,Q,S); 04700.xZ, 04703.xZ, 04704.xZ, 047C0.xZ, 047C0.x6, 047C3.x6, 047C3.xZ, 047C4.x6, 047C4.xZ, 047D0.x6, 047D0.xZ, 047D3.x6, 047D3.xZ, 047D4.x6, 047D4.xZ, 047E0.xZ, 047E3.x6, 047E3.xZ, 047E4.x6, 047E4.xZ, 047F0.x6, 047F0.xZ, 047F3.x6, 047F3.xZ, 047F4.x6, 047F4.xZ, 047H0.x6, 047H0.xZ, 047H3.x6, 047H3.xZ, 047H4.x6, 047H4.xZ, 047J0.x6, 047J0.xZ, 047J3.x6, 047J3.xZ, 047J4.x6, 047J4.xZ, 047K0.x6, 047K0.xZ, 047K3.x6, 047K3.xZ, 047K4.x6, 047K4.xZ, 047L0.x6, 047L0.xZ, 047L3.x6, 047L3.xZ, 047L4.x6, 047L4.xZ, 047M0.x6, 047M0.xZ, 047M3.x6, 047M3.xZ, 047M4.x6, 047M4.xZ, O47N0.x6, O47N0.xZ, O47N3.x6, O47N3.xZ, O47N4.x6, O47N4.xZ, O47P0.x6, O47P0.xZ, O47P3.x6, O47P3.xZ, O47P4.x6, O47P4.xZ, O47Q0.x6, O47Q0.xZ, O47Q3.x6, O47Q4.xZ, O47R0.xZ, O47R3.x6, O47R4.xZ, O47S0.xZ, O47S3.x6, O47S4.xZ, O47T0.xZ, O47T3.x6, O47T4.xZ, O47U0.xZ, O47U3.x6, O47U4.xZ, O47V0.xZ, O47V3.x6, O47V4.xZ, O47W0.xZ, O47W3.x6, O47W4.xZ, O47Y0.xZ, O47Y3.x6, O47Y4.xZ (where x =4,5,6,7,D,E,F,G,Z); 047K0.x1, 047K3.x1, 047K4.x1, 047L0.x1, 047L3.x1, 047L4.x1, 047M0.x1, 047M3.x1, 047M4.x1, O47N0.x1, O47N3.x1, O47N4.x1 (where x = 4,D,Z); 04700.x6, 04703.x6, 04704.x6, 047E0.x6 (where x = D,E,F,G,Z); 04CK0.Zx, 04CK3.Zx, 04CK4.Zx, 04CL0.Zx, 04CL3.Zx, 04CL4.Zx, 04CM0.Zx, 04CM3.Zx, 04CM4.Zx, 04CN0.Zx, 04CN3.Zx, 04CN4.Zx, 04CP0.Zx, 04CP3.Zx, 04CP4.Zx,	

	04CQ0.Zx, 04CQ3.Zx, 04CQ4.Zx, 04CR0.Zx, 04CR3.Zx, 04CR4.Zx, 04CS0.Zx, 04CS3.Zx, 04CS4.Zx, 04CT0.Zx, 04CT3.Zx, 04CT4.Zx, 04CU0.Zx, 04CU3.Zx, 04CU4.Zx, 04CV0.Zx, 04CV3.Zx, 04CV4.Zx, 04CW0.Zx, 04CW3.Zx, 04CW4.Zx, 04CY0.Zx, 04CY3.Zx, 04CY4.Zx (where x = Z,6); 04HC.xDZ, 04HD.xDZ, 04HE.xDZ, 04HF.xDZ, 04HH.xDZ, 04HJ.xDZ, 04HK.xDZ, 04HL.xDZ, 04HM.xDZ, 04HN.xDZ, 04HP.xDZ, 04HQ.xDZ, 04HR.xDZ, 04HS.xDZ, 04HT.xDZ, 04HU.xDZ, 04HV.xDZ, 04HW.xDZ, 04HY.xDZ, 04NC.xZZ , 04ND.xZZ , 04NE.xZZ , 04NF.xZZ , 04NH.xZZ , 04NJ.xZZ , 04NK.xZZ , 04NL.xZZ , 04NM.xZZ , 04NN.xZZ , 04NP.xZZ , 04NQ.xZZ , 04NR.xZZ , 04NS.xZZ , 04NT.xZZ , 04NU.xZZ, 04NV.xZZ,04NW.xZZ,04NY.xZZ (where x = 0,3,4). CPT/HCPCS: 35256, 35286, 35351, 35355, 35361, 35363, 35371-72, 35381, 35454, 35456, 35459, 35470, 35473-74, 35482-83, 35485, 35492-93, 35495, 35521, 35533, 35541, 35546, 35548-49, 35551, 35556, 35558, 35563, 35565, 35558, 35563, 35565, 35570-71, 35582-83, 35585, 35587, 35621, 35623, 35637-38, 35641, 35646-47, 35651, 35654, 35656, 35661, 35663, 35666, 35671, 35681-83, 35879, 37207-08, 37220-35	
Metformin **NB. TO DEFINE GRADE-LIKE POPULATION PLEASE USE ONLY THE NDC generic name "METFORMIN HCL" (see paragraph 8.3.1)**	NDC generic name: METFORMIN HCL, ALOGLIPTIN BENZOATE/METFORMIN HCL, REPAGLINIDE/METFORMIN HCL, CANAGLIFLOZIN/METFORMIN HCL, DAPAGLIFLOZIN PROPANEDIOL/METFORMIN HCL, LINAGLIPTIN/METFORMIN HCL, SAXAGLIPTIN HCL/METFORMIN HCL, ERTUGLIFLOZIN PIDOLATE/METFORMIN HCL, EMPAGLIFLOZIN/METFORMIN HCL, SITAGLIPTIN PHOSPHATE/METFORMIN HCL, ROSIGLITAZONE MALEATE/METFORMIN HCL, PIOGLITAZONE HCL/METFORMIN HCL, GLIPIZIDE/METFORMIN HCL, GLYBURIDE/METFORMIN HCL, METFORMIN HCL, EMPAGLIFLOZIN/LINAGLIPTIN/METFORMIN HCL	--
Exclusion criteria	**Codes**	
Nursing home	Claims in SNF dataset CPT codes: 99301, 99302, 99303, 99311, 99312, 99313, 99315, 99316, 99379, 99380, G0066 Place of service code: 31 (skilled nursing facility), 32 (nursing facility), 33 (custodial care facility)	Any setting, any position
Type 1 diabetes mellitus	ICD 9 diagnosis: 250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91, 250.93 ICD 10 diagnosis: E10.x	Any setting, any position
Secondary and gestational diabetes	ICD 9 diagnosis: 249.x, 648.8x ICD 10 diagnosis: E08.x, E09.x, O24.4x, O99.81	Any setting, any position
Insulin	ICD 9 diagnosis: V58.67 ICD 10 diagnosis: Z79.4 NDC generic name: INSULIN DEGLUDEC/LIRAGLUTIDE; INSULIN GLARGINE,HUMAN RECOMBINANT ANALOG/LIXISENATIDE; INSULIN INHALATION CHAMBER; INSULIN ISOPHANE,BEEF PURE; INSULIN NPH HUMAN SEMI-SYNTHETIC; INSULIN PROTAMINE ZINC,BEEF; INSULIN PROTAMINE ZN,PORK (P); INSULIN REG HUMAN SEMI-SYN; INSULIN REGULAR,HUMAN BUFFERED; INSULIN RELEASE UNIT; INSULIN ZINC EXT,BEEF (P); INSULIN ZINC EXTENDED HUMAN RECOMBINANT; INSULIN ZINC EXTENDED,BEEF; INSULIN ZINC HUMAN SEMI-SYN; INSULIN ZINC PROMPT,BEEF; INSULIN ZINC PROMPT,BF-PK; INSULIN ZINC PROMPT,PORK PURE; INSULIN,BEEF; INSULIN,PORK	

	PURIFIED/INSULIN ISOPHANE,PORK PURE; INSULIN GLULISINE; INSULIN POWDER INHALER/INSULIN INHALATION CHAMBER; INSULIN PROTAMINE ZN,BEEF (P); INSULIN PUMP CONTROLLER; INSULIN PUMP/INFUSION SET/BLOOD-GLUCOSE METER; INSULIN REGULAR, HUMAN/INSULIN RELEASE UNIT/CHAMBER/INHALER; INSULIN ZINC,BEEF PURIFIED/INSULIN ZINC,PORK PURIFIED; INSULIN,PORK REG. CONCENTRATE; INSULIN ASPART (NIACINAMIDE); INSULIN DEGLUDEC; INSULIN ISOPHANE,BEEF; INSULIN NPH HUMAN AND INSULIN REGULAR HUMAN SEMI-SYNTHETIC; INSULIN REG, HUM S-S BUFF; INSULIN REGULAR, HUMAN/INSULIN RELEASE UNIT; INSULIN ZINC BEEF; INSULIN ZINC,PORK PURIFIED; INSULIN,PORK; INSULIN ISOPHANE NPH,BF-PK; INSULIN LISPRO-AABC; INSULIN PROTAMINE ZN,BF-PK; INSULIN ZINC EXTENDED,BF-PK; INSULIN ZINC HUMAN RECOMBINANT; INSULIN ZINC,BEEF PURIFIED; INSULIN ZINC,BEEF-PORK; INSULIN ISOPHANE,PORK PURE; INSULIN PUMP SYRINGE, 1.8 ML; INSULIN REGULAR,BEEF-PORK; INSULIN DETEMIR; INSULIN ASPART PROTAMINE HUMAN/INSULIN ASPART; INSULIN,PORK PURIFIED; INSULIN PUMP SYRINGE, 3 ML; INSULIN ASPART; INSULIN PUMP CARTRIDGE; INSULIN LISPRO PROTAMINE AND INSULIN LISPRO; INSULIN GLARGINE,HUMAN RECOMBINANT ANALOG; INSULIN NPH HUMAN ISOPHANE; INSULIN LISPRO; INSULIN NPH HUMAN ISOPHANE/INSULIN REGULAR, HUMAN; INSULIN REGULAR, HUMAN	
End-stage renal disease (including dialysis or renal transplant)	ICD-9 diagnosis: 585.5, 585.6, 996.81, V42.0, V45.1x, V56.xx ICD-9 procedure: 39.95, 54.98, 55.6x ICD-10 diagnosis: N18.5, N18.6, R88.0, T82.41x, T82.42x, T82.43x, T82.49x, T85.611x, T85.621x, T85.631x, T85.71x, T86.1x, Y84.1, Z48.22, Z49.xx, Z91.15, Z94.0, Z99.2 ICD-10 procedure: 0TY00Zx, 0TY10Zx, 3E1M39Z, 5A1Dx0Z HCPCS/CPT: 50360, 50365, 90920, 90921, 90924, 90925, 90935, 90937, 90939, 90940, 90945, 90947, 90957, 90958, 90959, 90960, 90961, 90962, 90965, 90966, 90969, 90970, 90989, 90993, 90999, 90997, 99512, 99559, 99512, G0257, G0314, G0315, G0316, G0317, G0318, G0319, G0322, G0323, G0326, G0327, S9335, S9339	Any setting, any position
Acute or chronic pancreatitis	ICD 9 diagnosis: 577.0, 577.1 ICD 10 diagnosis: K85.x, K86.0, K86.1	Any setting, any position
Cirrhosis or acute hepatitis	**Cirrhosis** ICD-9 diagnosis: 571.2, 571.5, 571.6 ICD-10 diagnosis: K70.11, K70.2, K70.3x, K70.4x, K71.7, K74.x (excluding K74.0x, K74.1, K74.2) **Acute hepatitis** ICD-9 diagnosis: 070.20, 070.21, 070.30, 070.31, 070.41, 070.51, 571.1 ICD-10 diagnosis: B16.0, B16.1, B16.2, B16.9, B17.0, B17.10, B17.11, B17.2, B17.8, B17.9, K71.2	Any setting, any position
MEN-2 or history of medullary thyroid cancer	ICD-9 diagnosis: 258.02, 258.03 ICD-10 diagnosis: E31.22, E31.23	Any setting, any position
Organ transplant	ICD-9 diagnosis: V42.1x, V42.6x, V42.7x, V42.8x (except for V42.81 or V42.82), V42.9x, V58.44, E878.0x ICD-9 procedure: 33.5x, 33.6x, 37.51, 46.97, 50.5x, 52.8x, 55.6x, 996.8x (except for 996.85 or 996.88), V42.0x	Any setting, any position

	ICD-10 diagnosis: T86.1xx-T86.4xx, T86.81x, T86.85x, T86.89x, T86.9xx, Y83.0x, Z48.2xx (except for Z48.290), Z94.0x-Z94.4x, Z94.82, Z94.83, Z94.89, Z94.9x ICD-10 procedure: 02YAxxx, 0BYCxxx-0BYMxxx, 0DY5xxx, 0DY6xxx, 0DY8xxx, 0DYExxx, 0FSGxxx, 0FY0xxx, 0FYGxxx, 0TY0xxx, 0TY1xxx, 3E030Ux, 3E033Ux, 3E0J3Ux, 3E0J7Ux, 3E0J8Ux CPT/HCPCS: 32851-32854, 33935, 33945, 44135, 44136, 47135, 47136, 48554, 48556, 50360, 50365, 50370, 50380	

Table a2. Primary effectiveness outcomes

Outcome	Components	Diagnosis and/or Procedure Codes	Setting/Position
MACE	MI	ICD-9 diagnosis: 410.x ICD-10 diagnosis: I21.x (excluding I21.9, I21.Ax)	Inpatient, primary or secondary position
	Stroke	ICD-9 diagnosis: 430, 431, 433.x1, 434.x1, 436 ICD-10 diagnosis: I60.x, I61.x, I63.x, I67.89	Inpatient, primary position
	CV mortality	***Medicare & VHA*** NDI ICD-10 Cause of CV Death Code: I00.x - I99.x ***CPRD*** Read/SNOMED codes and ICD codes	Primary cause of death
Modified MACE	MI	Same definition reported for the MACE outcome	
	Stroke	Same definition reported for the MACE outcome	
	All-cause mortality	***Medicare*** Vital Status File & NDI ICD-10 Cause of Death when available ***CPRD*** Read/SNOMED codes and ICD codes ***VHA*** NDI ICD-10 Cause of Death	
Hospitalized Heart Failure (HHF)	--	ICD-9 diagnosis: 428.xx, 398.91, 402.x1, 404.x1, 404.x3 ICD-10 diagnosis: I09.81, I11.0, I13.0, I13.2, I50.xxx	Inpatient, primary position

Note. Please provide also results for HHF outcome defined as above but with diagnosis codes in any position.

Table a3. Secondary effectiveness outcomes

Outcomes	Diagnosis and/or Procedure Codes	Setting/Position
MI	Definition provided in Table a1	
Stroke	Definition provided in Table a1	
CV mortality	Definition provided in Table a1	
All-cause mortality	Definition provided in Table a1	
Coronary revascularization	ICD-9 procedure: 00.66, 36.03, 36.06, 36.07, 36.09, 36.1x, 36.2x, 36.3x ICD-10 procedure: 0210.xxx, 0211.xxx, 0212.xxx, 0213.xxx, 021K0Z5, 021K4Z5, 021L0Z5, 021L4Z5, 0270.xxx, 0271.xxx, 0272.xxx, 0273.xxx, 02C0.xxx, 02C1.xxx, 02C2.xxx, 02C3.xxx, 02QA.xxx, 02QB.xxx, 02QC.xxx CPT/HCPCS: 33140, 33141, 33510-33536, 33545, 33572, 92920, 92921, 92924, 92925, 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, 92944, 92973, 92980, 92981, 92984, 92995, 92996	Inpatient, any position

Table a4. Safety outcomes

Outcomes	Component	Diagnosis and/or Procedure Codes	Setting/Position
Diabetic ketoacidosis (DKA)	--	ICD-9 diagnosis: 250.1x ICD-10 diagnosis: E10.1x, E11.1x, E13.1x	Inpatient, primary position
Bone fractures	Humerus	Case qualifying (CQ) = 1 Diagnosis (ICD-9: 812.x, 733.11; ICD-10: M80.02xA, M80.82xA, M84.42xA, M84.62xA, S42.xxxA, S42.xxxB, S42.xxxC) **OR** CQ = 2 Diagnosis (ICD-9: 812.x, 733.11; ICD-10: M80.02xA, M80.82xA, M84.42xA, M84.62xA, S42.xxxA, S42.xxxB, S42.xxxC) **AND (overlapping)** Procedure (ICD-9: 78.52, 79.01, 79.11, 79.21, 79.31, 79.61; ICD-10: 0PHCx, 0PHDx, 0PHFx 0PHGx, OPSDx, OPSEx, OPSFx, OPSGx; CPT-4: 23600, 23605, 23610, 23615, 23620, 23625, 23630, 23665, 23670, 23680, 24500, 24505, 24510, 24515, 24530, 24531, 24535, 24536, 24538, 24540, 24542, 24545, 24560, 24565, 24575, 24586, 24587, 24588, 24516)	Inpatient, any position Non-inpatient, any position
	Radius/ulna	CQ = 1 Diagnosis (ICD-9: 813.x, 733.12; ICD-10: M80.03xA, M80.83xA, M84.43xA, M84.63xA, S52.xxxA, S52.xxxB, S52.xxxC) **OR** CQ = 2 Diagnosis (ICD-9: 813.x, 733.12; ICD-10: M80.03xA, M80.83xA, M84.43xA, M84.63xA, S52.xxxA, S52.xxxB, S52.xxxC) **AND (overlapping)** Procedure (ICD-9: 78.53, 79.02, 79.12, 79.22, 79.32, 79.62; ICD-10: 0PHHx, 0PHKx, 0PHJx, 0PHLx, 0PSHx, 0PSKx, 0PSJx, 0PSLx; CPT-4: 24620, 24635, 24650, 24655, 24660, 24665, 24666, 24670, 24680, 24685, 25500, 25505, 25510, 25515, 25530, 25535, 25540, 25545, 25560, 25565, 25570, 25575, 25600, 25605, 25610, 25611, 25615, 25620, 25650)	Inpatient, any position Non-inpatient, any position
	Hip	CQ = 1 Diagnosis [ICD-9: 820.x (excl. 820.01, 820.11), 821.x (excl. 821.32, 820.11), 733.14, 733.15, 733.96, 733.97; ICD 10: M80.05xA, M80.85xA, M84.35xA (excl. M84.350x), M84.45xA (excl. M84.454x), M84.65xA (excl. M84.650x), M84.75xA, S72.xxxA, S72.xxxB, S72.xxxC (excl. S72.02x, S72.44x)] **OR** CQ = 2 Diagnosis [ICD-9: 820.x (excl. 820.01, 820.11), 821.x (excl. 821.32, 820.11), 733.14, 733.15, 733.96, 733.97; ICD 10: M80.05xA, M80.85xA, M84.35xA (excl. M84.350x), M84.45xA (excl. M84.454x), M84.65xA (excl. M84.650x), M84.75xA, S72.xxxA, S72.xxxB, S72.xxxC (excl. S72.02x, S72.44x)] **AND (overlapping)** Procedure (ICD-9: 78.55, 79.05, 79.15, 79.25, 79.35, 79.65; ICD-10: 0QH6x, 0QH7x, 0QH8x, 0QH9x, 0QHBx, 0QHCx, 0QS6x, 0QS7x, 0QS8x, 0QS9x, 0QSBx, 0QSCx; CPT: 27230, 27232, 27235, 27236, 27238, 27240, 27244, 27245, 27246, 27248, 27267, 27268, 27269, 27125, 27130**,** 27500, 27503, 27508, 27509, 27513, 27501, 27502, 27506, 27507, 27514, 27254)	Inpatient, any position Non-inpatient, any position
	Pelvis	CQ = 1 Diagnosis (ICD-9: 808.x, 733.98; ICD-10: ICD 10 diagnosis: M84.350xA, M84.454xA, M84.650xA, S32.3xxA, S32.3xxB, S32.4xxA, S32.4xxB, S32.5xxA, S32.5xxB, S32.6xxA, S32.6xxB, S32.8xxA, S32.8xxB, S32.9xxA, S32.9xxB) **OR** CQ = 2 Diagnosis (ICD-9: 808.x, 733.98; ICD-10: ICD 10 diagnosis: M84.350xA, M84.454xA, M84.650xA, S32.3xxA, S32.3xxB, S32.4xxA, S32.4xxB, S32.5xxA, S32.5xxB, S32.6xxA, S32.6xxB, S32.8xxA, S32.8xxB, S32.9xxA, S32.9xxB) **AND (overlapping)** Procedures (CPT/ HCPCS: 27193, 27194, 27200, 27202, 27215, 27216, 27217, 27218, 27220, 27222, 27226, 27227, 27228, G0412, G0413, G0414, G0415)	Inpatient, any position Non-inpatient, any position

Lower-limb amputations	--	ICD-9 procedure: 84.1x (excluding 84.18, 84.19) ICD-10 procedure: 0Y.6x (excluding 0Y.62, 0Y.63, 0Y.64) CPT: 27590, 27591, 27592, 27880, 27881, 27882, 27884, 27886, 27888, 27889, 28800, 28805, 28810, 28820, 28825, 27594, 27596, 27598	Inpatient or non-inpatient, any position
Acute kidney injury (AKI)	--	ICD-9 diagnosis: 584.x ICD-10 diagnosis: N17.x	Inpatient, any position
Urinary tract infections (UTI)	Primary UTI	ICD-9 diagnosis: 590.xx, 595.xx, 597.xx, 599.0x ICD-10 diagnosis: N10-N12, N13.6, N30.x, N34.x, N39.0	Inpatient, primary position
	Sepsis and UTI	ICD-9 diagnosis: 590.x, 595.x, 597.x, 599.0x ICD-10 diagnosis: N10-N12, N13.6, N30.x, N34.x, N39.0 **AND (within the same inpatient discharge)** ICD-9 diagnosis: 038.x, 785.52, 790.7, 995.9x ICD-10 diagnosis: A40.x, A41.x, R65.21, R78.81, R65.x	Inpatient, any position
	Pyelonephritis	ICD-9 diagnosis: 590.xx ICD-10 diagnosis: N10-N12, N13.6	Inpatient, any position
Genital infections^	--	ICD-9 diagnosis: 112.1, 616.1x, 112.2, 607.1, 112.2, 605 ICD-10 diagnosis: B37.3, N77.1, N76.0-N76.3, B37.49, B37.42, N48.1, N47.6, B37.49, N47.x (except N47.0, N47.6)	Any setting, any position
Acute pancreatitis	--	ICD-9 diagnosis: 577.0 ICD-10 diagnosis: K85.x	Inpatient, primary position
Biliary events	--	ICD-9 diagnosis: 574.x, 575.x, 576.x, 560.31, 571.6, 155.1, 156.x, 235.3, 230.8 ICD-10 diagnosis: K80.x, K81.x, K82.x, K83.x, K85.1x, K87, K56.3, K74.3, C22.1, C23, C24.x, D37.6, D01.5	
Severe hypoglycemia	--	ICD-9 diagnosis: 251.0, 251.1, 251.2, 962.3 ICD-10 diagnosis: E10.641, E10.649, E11.641, E11.649, E13.641, E13.649, E15, E16.0, E16.1, E16.2, T38.3X1A, T38.3X1D, T38.3X1S, T38.3X2A, T38.3X2D, T38.3X2S, T38.3X3A, T38.3X3D, T38.3X3S, T38.3X4A, T38.3X4D, T38.3X4S, T38.3X5A, T38.3X5D, T38.3X5S **OR** ICD-9 diagnosis: 251.0, 251.1, 251.2, 962.3 ICD-10 diagnosis: E10.641, E10.649, E11.641, E11.649, E13.641, E13.649, E15, E16.0, E16.1, E16.2, T38.3X1A, T38.3X1D, T38.3X1S, T38.3X2A, T38.3X2D, T38.3X2S, T38.3X3A, T38.3X3D, T38.3X3S, T38.3X4A, T38.3X4D, T38.3X4S, T38.3X5A, T38.3X5D, T38.3X5S	Inpatient, primary position Emergency Department (ED), any position
Short-term retinopathy	Intravitreal anti-VEGF injection	CPT: 67028 **AND (within the same day)** HCPCS: C9291, J0178, J2778, Q2046, C9257, Q5107, J9035, C9296, J9400	Any setting, any position
	Panretinal photo-coagulation	CPT: 67228	
	Onset of vitreous hemorrage	ICD-9 diagnosis: 379.23 ICD-10 diagnosis: H43.1x	
	Proliferative diabetic retinopathy	ICD-9 diagnosis: 362.02 ICD-10 diagnosis: E11.35x	

^ findings for genital infections might be stratified by gender in a secondary analysis

Note. Please provide also results for DKA and AKI outcomes defined as above but with diagnosis codes in any position and primary position respectively.

Definitions of effectiveness and safety outcomes are based on the following studies:

MACE and its components

- Kiyota Y, Schneeweiss S, Glynn RJ, Cannuscio CC, Avorn J, Solomon DH. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. Am Heart J 2004;148:99–104.
- Wahl PM, Rodgers K, Schneeweiss S, et al. Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population. Pharmacoepidemiol Drug Saf 2010;19:596–603.
- Tirschwell DL, Longstreth WT Jr. Validating administrative data in stroke research. Stroke 2002;33:2465–2470.
- Olubowale OT, Safford MM, Brown TM, et al. Comparison of expert adjudicated coronary heart disease and cardiovascular disease mortality with the national death index: results from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study. J Am Heart Assoc 2017;6:e004966.
- Patorno E, Pawar A, Franklin JM, Najafzadeh M, Déruaz-Luyet A, Brodovicz KG, Sambevski S, Bessette LG, Santiago Ortiz AJ, Kulldorff M, Schneeweiss S. Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care. Circulation. 2019 Jun 18;139(25):2822-2830.

Hospitalized Heart Failure

- Saczynski JS, Andrade SE, Harrold LR, et al. A systematic review of validated methods for identifying heart failure using administrative data. Pharmacoepidemiol Drug Saf 2012;21(Suppl. 1):129–140.
- Patorno E, Pawar A, Franklin JM, Najafzadeh M, Déruaz-Luyet A, Brodovicz KG, Sambevski S, Bessette LG, Santiago Ortiz AJ, Kulldorff M, Schneeweiss S. Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care. Circulation. 2019 Jun 18;139(25):2822-2830.

Coronary revascularization

- Wahl PM, Rodgers K, Schneeweiss S, et al. Validation of claims-based diagnostic and procedure codes for cardiovascular and gastrointestinal serious adverse events in a commercially-insured population. Pharmacoepidemiol Drug Saf 2010;19:596–603.
- Patorno E, Pawar A, Franklin JM, Najafzadeh M, Déruaz-Luyet A, Brodovicz KG, Sambevski S, Bessette LG, Santiago Ortiz AJ, Kulldorff M, Schneeweiss S. Empagliflozin and the Risk of Heart Failure Hospitalization in Routine Clinical Care. Circulation. 2019 Jun 18;139(25):2822-2830.

Diabetic ketoacidosis

- Fralick M, Schneeweiss S, Patorno E. Risk of Diabetic Ketoacidosis after Initiation of an SGLT2 Inhibitor. N Engl J Med. 2017 Jun 8;376(23):2300-2302.
- Bobo WV, Cooper WO, Epstein RA Jr., Arbogast PG, Mounsey J, Ray WA. Positive predictive value of automated database records for diabetic ketoacidosis (DKA) in children and youth exposed to antipsychotic drugs or control medications: a Tennessee Medicaid Study. BMC Med Res Methodol 2011;11:157.

Bone fractures

- Wright NC, Daigle SG, Melton ME, Delzell ES, Balasubramanian A, Curtis JR. The Design and Validation of a New Algorithm to Identify Incident Fractures in Administrative Claims Data. J Bone Miner Res. 2019;34(10):1798-1807.
- Ray WA, Griffin MR, Fought RL, Adams ML. Identification of fractures from computerized Medicare files. Journal of clinical epidemiology 1992;45:703-14.

- Hudson M, Avina-Zubieta A, Lacaille D, Bernatsky S, Lix L, Jean S. The validity of administrative data to identify hip fractures is high--a systematic review. Journal of clinical epidemiology 2013;66:278-85.

Lower-limb amputations
- Fralick M, Kim SC, Schneeweiss S, Everett BM, Glynn RJ, Patorno E. Risk of amputation with canagliflozin across categories of age and cardiovascular risk in three US nationwide databases: cohort study. BMJ. 2020 Aug 25;370:m2812.
- Newton KM, Wagner EH, Ramsey SD, et al. The use of automated data to identify complications and comorbidities of diabetes: a validation study. J Clin Epidemiol1999;52:199-207.

Acute kidney injury
- Patorno E, Pawar A, Bessette LG, Kim DH, Dave C, Glynn RJ, Munshi MN, Schneeweiss S, Wexler DJ, Kim SC. Comparative Effectiveness and Safety of Sodium-Glucose Cotransporter 2 Inhibitors Versus Glucagon-Like Peptide 1 Receptor Agonists in Older Adults. Diabetes Care. 2021 Mar;44(3):826-835. [see validation study 2006]

Urinary tract infections
- Dave CV, Schneeweiss S, Kim D, Fralick M, Tong A, Patorno E. Sodium-Glucose Cotransporter-2 Inhibitors and the Risk for Severe Urinary Tract Infections: A Population-Based Cohort Study. Ann Intern Med. 2019 Aug 20;171(4):248-256.

Genital infections
- Dave CV, Schneeweiss S, Patorno E. Comparative risk of genital infections associated with sodium-glucose co-transporter-2 inhibitors. Diabetes Obes Metab. 2019 Feb;21(2):434-438.

Acute pancreatitis
- Moores K, Gilchrist B, Carnahan R, Abrams T. A systematic review of validated methods for identifying pancreatitis using administrative data. Pharmacoepidemiol Drug Saf. 2012 Jan;21 Suppl 1:194-202.

Biliary events
- Faillie JL, Yu OH, Yin H, Hillaire-Buys D, Barkun A, Azoulay L. Association of Bile Duct and Gallbladder Diseases With the Use of Incretin-Based Drugs in Patients With Type 2 Diabetes Mellitus. JAMA Intern Med. 2016 Oct 1;176(10):1474-1481.

Severe hypoglycemia
- Min JY, Presley CA, Wharton J, Griffin MR, Greevy RA Jr, Hung AM, Chipman J, Grijalva CG, Hackstadt AJ, Roumie CL. Accuracy of a composite event definition for hypoglycemia. Pharmacoepidemiol Drug Saf. 2019 May;28(5):625-631.
- Karter AJ, Warton EM, Moffet HH, Ralston JD, Huang ES, Miller DR, Lipska KJ. Revalidation of the Hypoglycemia Risk Stratification Tool Using ICD-10 Codes. Diabetes Care. 2019 Apr;42(4):e58-e59

Short-term retinopathy
- Due to the lack of a validated claims-based algorithm to identify patients with short-term retinopathy, the current definition was ultimately built after extensive discussion within the research group and experts' consultation (mainly ophthalmologists that studied retinopathy).

Table a5. Overall list of covariates.

Demographics
Age
Gender
Calendar year of cohort entry
Geographic region (i.e., Midwest, Northeast, South, West, others)
Race (i.e., white, black, others)
Alcohol dependence
Drug dependence
Obesity
Overweight
Smoking status
Diabetes related variables
Diabetic nephropathy
Diabetic retinopathy
Diabetes ophthalmic manifestation
Diabetic neuropathy
Diabetic peripheral circulatory disorders
Diabetic foot
Infection of lower extremities
Lower limb amputation
Erectile dysfunction
Hypoglycemia
Hyperglycemia
Diabetic ketoacidosis
Hyperosmolar hyperglycemic nonketotic syndrome
Diabetes with other complications
Diabetes without mention of complications
Duration of diabetes (when available)
Number of HbA1c tests ordered
Number of glucose tests or monitoring ordered
Number of antidiabetic drugs used at cohort entry
No previous use of other antidiabetic drugs
Other comorbidities
Cancer
Acute myocardial infarction
Old myocardial infarction
Myocardial infarction sequelae
Unstable angina
Stable angina
Coronary atherosclerosis
Coronary procedure
History of coronary procedure
Congestive heart failure
Stroke
Cerebrovascular procedure
Generalized and unspecified atherosclerosis

Atherosclerotic cerebrovascular disease
Peripheral arteriopathy
Peripheral arterial procedure
Lower-limb amputations
Cardiomyopathy
Cardiac valve disorder
Atrial fibrillation
Chronic kidney disease
stage 1-2
stage 3-4
unspecified
Acute kidney injury
Hypertensive nephropathy
Proteinuria
Urinary tract infection
Miscellaneous renal disease
Kidney or urinary stone
Disorders of electrolyte
Disorders of fluid balance
Liver diseases (including cirrhosis, non-alcoholic steatohepatitis or fatty liver disease, other liver diseases)
COPD
Pneumonia
Asthma
Dementia
Hyperlipidemia
Hypertension
Ischemic heart disease
Coronary revascularization
Other cardiac dysrhythmias
Conduction disorder
Transient ischemic attack
Major bleeding
Edema
Pneumonia
Obstructive sleep apnea
Osteoarthritis
Osteoporosis
Fractures
Falls
Hypothyroidism
Other disorders of thyroid gland
Depression
Anxiety or sleep disorder
Venous thromboembolism
Indexes of general comorbidity and frailty
Combined comorbidity score
Frailty score Index

Measures of health care utilization
Number of hospitalizations
Number of days spent hospitalized
Number of emergency department visits
Number of outpatient visits
Number of unique non-antidiabetic medication classes
Number of antidiabetic medications used at cohort entry (days' supply overlap with cohort entry date)
Number of visits to endocrinologist
Number of visits to cardiologist
Number of visits to internist
Number of visits to nephrologist
Number of electrocardiograms received
Number of echocardiograms received
Number of stress tests received
Number of preventive services received
Number of creatinine tests ordered
Number of lipid tests ordered
Number of microalbuminuria tests ordered
Number of metabolic or renal/creatinine tests ordered
Measures of socioeconomic status
Inpatient total costs
Outpatient total costs
Ratio of brand vs generic medications
Dual eligibility with Medicare (e.g., Medicare Advantage program)
Low-income subsidies (CMS)
Out of pocket pharmacy cost
Medications
Metformin
Sulfonylurea
Thiazolidinediones
Meglitinides
α-glucosidase inhibitors
DPP-4i
GLP-1 ra
SGLT-2i
Insulin
ACE inhibitors
Angiotensin II receptor blockers
Beta blockers
Calcium channel blockers
Thiazides
Loop diuretics
Mineralocorticoid receptor antagonists
Nitrates
Other antihypertensives
Digoxin
Antiarrhythmics

COPD/asthma medications (beta 2 agonist inhalant, anticholinergic inhalant, glucocorticoid inhalant)
Oral corticosteroids
Osteoporosis medications
Statins
Other lipid-lowering drugs
Anticoagulants
Antiplatelets
NSAIDs
Opioids
Gabapentinoids
Urinary tract infection antibiotics
Antidepressants
Benzodiazepines
Other anxiolytics or hypnotics
Antipsychotics
Antiparkinsonian medications
Dementia medication
Laboratory values (when available)
HbA1c
Glucose
Urine Albumin-Creatinine Ratio
Proteinuria
eGFR
Total cholesterol
LDL
HDL
Triglyceride level

Abbreviations: COPD, chronic obstructive pulmonary disease; DPP-4i, dipeptidyl peptidase 4 inhibitors; GLP-1 ra, glucagon-Like Peptide 1 Receptor Agonists; SGLT-2i, sodium-glucose cotransporter 2 inhibitors; ACEi, angiotensin-converting enzyme inhibitor; eGFR, estimated Glomerular Filtration Rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein.